Use of 1,3-Dioxin-4-ones and Related Compounds in Synthesis. 46. 2-(*l*-Menthyloxycarbonyl)-2,6-dimethyl-1,3-dioxin-4-one and Related Compounds. Relationship between Facial Selectivity and Pyramidalization[1]

Masayuki Sato,*,† Masayuki Murakami,† Satoshi Sunami,† Chikara Kaneko,*,† Toshio Furuya,‡ and Hiroyuki Kurihara‡

Contribution from the Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980–77, Japan, and Tsukuba Research Laboratory, Yamanouchi Pharmaceutical Company, Ltd., Miyukigaoka, Tsukuba, Ibaraki 305, Japan

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Abstract: Preparation and ground-state reactions (conjugate addition and catalytic hydrogenation) of a 1,3-dioxin-4-one having an *l*-menthyloxycarbonyl group at the 2-position as the only substituent (**7a**) and its 6-methyl derivative (**8a**), as well as their 2-methyl derivatives (**5a** and **6a**), are reported. The X-ray structure of the 2-(methoxycarbonyl)-2-phenyl derivative (**4b**) was also determined. The result, when combined with previously reported X-ray crystallographic analyses on related dioxinones, suggests that all of the dioxinones take a sofa conformation of the six-membered ring, whose top face is always on the same side as the pyramidalization of the enone function in the ring. Conjugate addition reaction of **5a** leads to exclusive addition on the bottom face, while addition to **7a** gives the product corresponding to the top face addition. Catalytic hydrogenation of **6a** and **8a** is also reported. Though the selectivity is much lowered as compared with the conjugate addition, the same facial selectivities are again observed. A comparison with the exclusive top face attack on 2-*tert*-butyl-1,3-dioxin-4-one (**1**) and its 2-methyl derivative **2** and bottom face attack on 2-(*l*-menthyloxycarbonyl)-2-phenyl-1,3-dioxin-4-one (**3a**) makes it clear that the prediction of facial selectivity in these ground-state reactions (conjugate addition and catalytic hydrogenation) based on pyramidalization is not always correct. A novel hypothesis which accounts for all of the above results (sofa conformation of the hetero ring, pyramidalization at the enone portion, and facial selectivity) is presented.

Introduction

Seebach et al. demonstrated that conjugate addition reactions with dialkylcuprates and catalytic hydrogenation of 2-*tert*-butyl-6-methyl-1,3-dioxin-4-one (**1**) both gave the products in which the nucleophile was introduced on the same face of the ring as the acetal hydrogen on C(2).[2] Later, Lange et al. reported that dialkylcuprate additions to 2-*tert*-butyl-2,6-dimethyldioxin-4-one (**2**) gave a single diasteromer, in which the nucleophile was again introduced on the same face of the ring as the acetal methyl group on C(2).[3] Both groups have concluded that, based on a sofa conformation of the hetero ring having the bulkier substituent in an equatorial orientation (verified by X-ray crystallographic structure determinations), the top face preference is due to pyramidalization (again verified by X-ray analysis) of the enone portion to the top face (throughout this paper, we refer to facial selectivity in terms of the top and bottom faces relative to the sofa conformation). We have found, in contrast, that the dioxinone **3** when subjected to the same reaction gave exclusively the product in which the reagent was introduced from the bottom face.[4] Though X-ray crystallographic analysis of **3a** verified the sofa conformation, no information concerning pyramidalization at C(6) was obtained due to the absence of a substituent at that position. Our aim in this study was to synthesize dioxinones having an alkoxycarbonyl group at the 2-position (**4**–**8**) and to examine the conjugate addition to **5** and **7** and the catalytic hydrogenation of **6** and **8**. We further planned to examine the pyramidalization at C(6) in the dioxinone **4** by means of X-ray crystallographic analysis of **4** to develop an explanation of the origin of the pyramidalization (if it can still be found in **4**) and to correlate the conformational features of dioxinones with the facial selectivities.

Chart 1

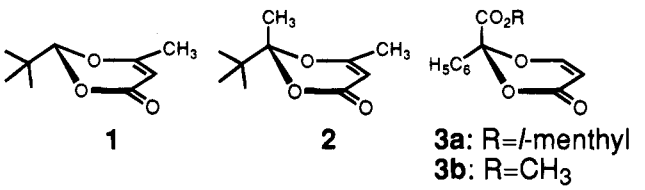
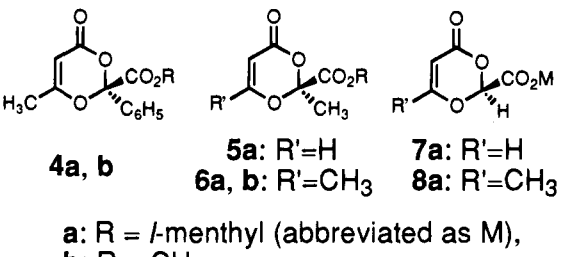


Chart 2



† Tohoku University.

‡ Yamanouchi Pharmaceutical Co., Ltd.

⊗ Abstract published in *Advance ACS Abstracts*, March 15, 1995.

(1) For Part 45, see: Sato, M.; Sunami, S.; Kaneko, C.; Satoh, S.; Furuya, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1665–1668.

(2) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763–4772.

(3) Organ, M. G.; Froese, R. D. J.; Goddard, J. D.; Taylor, N. J.; Lange, G. L. *J. Am. Chem. Soc.* **1994**, *116*, 3312–3323.

(4) Sato, M.; Murakami, M.; Kaneko, C.; Furuya, T. *Tetrahedron* **1993**, *49*, 8529–8540.

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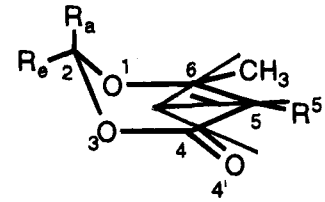
Results and Discussion

Preparation of Dioxinones 4−8 and Crystallographic Analysis of 4b. All dioxinones (**a** series as the *l*-menthyl esters and **b** series as the methyl esters) were prepared by application of the general synthetic procedure previously developed in our laboratory.[5] Thus, for the 6-unsubstituted dioxinones **5a** and **7a**, the *l*-menthyl α-oxo esters (*l*-menthyl pyruvate[6] or glyoxylate[7]) were reacted with the formylketene generated *in situ* from 5-formyl-2,2-dimethyl-1,3-dioxane-4,6-dione (formylated Meldrum's acid) (**9**)[8] by refluxing in toluene[9,10] and, for the 6-methyldioxinones **4a**, **6a**, and **8a**, *l*-menthyl phenylglyoxylate[6] and the same two α-oxo esters mentioned above were reacted with acetylketene generated *in situ* either from 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (acetylated Meldrum's acid) (**10**)[11] by refluxing in toluene or from 2,2,6-trimethyl-1,3-dioxin-4-one (**11**)[12] by refluxing in toluene. Though in all cases 1:1 mixtures of two diastereomers were obtained, the two isomers could be separated simply by fractional recrystallization. Throughout this paper, the diastereomers are defined as *R* and *S* on the basis of the configuration of the acetal carbon. The ^{1}H-NMR spectra of both diastereomers of **4a**, **5a**, and **6a** show that the alkoxycarbonyl groups in them take an axial orientation.[13,14] However, those of **7a** and **8a** take an equatorial orientation.[15] The configurations of the acetal carbon were then determined as depicted in Table 2, based on the following chemical transformation to known enantiomerically pure compounds. In essentially the same manner, the corresponding methyl esters **4b** and **6b** were synthesized in racemic form.

After examining a series of newly synthesized dioxinones **4−8**, we selected **4b** for X-ray structure determination. For measurement of the extent of pyramidalization, we employed the method proposed by Lange et al.[3] Thus, the pyramidalization is defined relative to a plane formed by the formally sp^2 hybridized atoms C-4, C-5, and C-6 with the substituents attached to those atoms being above (a) or below (b) the plane by an angle θ (Table 1).

Table 1 summarizes the pyramidalization found by X-ray crystallographic analyses of two dioxinones **1** and **2** and the newly synthesized dioxinone **4b**. It is clear that the sp^2 carbons at the 4- and 6-positions in ail these dioxinones are pyramidalized in the same direction (the top side) with comparable magnitude. It is therefore obvious that even the facial selectivity

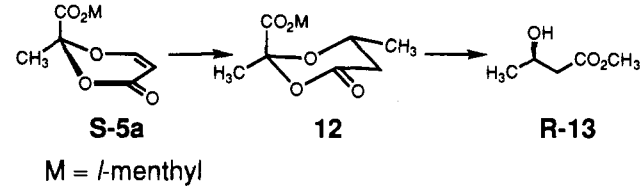
Table 1. Comparison of the Degree of Pyramidalization in 1,3-Dioxinones[a]



compd	R_e	R_a	R^5	C(4)−O(4′)	C(6)−CH_3
1[b]	*t*-Bu	H	Br	12.57	11.85
2[b]	*t*-Bu	CH_3	H	6.86	5.89
4b[c]	C_6H_5	CO_2CH_3	H	12.40	6.82
				15.30	13.78

[a] The positions of CH_3 and O(4′) are shown, with the degrees of pyramidalization at C(4) and C(6). [b] Data reported in Lange's paper (ref 3). The original X-ray data of **1** are given in ref 2. [c] Crystallized with two independent molecules (1:1) in the unit cell.

Scheme 1



S-5a **12** **R-13**

M = *l*-menthyl

observed in the conjugate addition reactions cannot be explained simply in terms of either pyramidalization or sofa conformation. With these data in mind, we then examined some ground-state reations of **5−8**.

Reactions of 5 and 6. Reaction of (*S*)-**5a** with MeMgBr/CuI gave **12a** in 70% yield as the sole product. Compound **12a** was converted to methyl (*R*)-3-hydroxybutanoate [(*R*)-**13**][16] by basic hydrolysis followed by methylation. Thus, the product formed resulted from attack of the cuprate reagent on the bottom face of (*S*)-**5a**.

Though the catalytic hydrogenation of **6a** did not proceed at atmospheric pressure, both diastereomers gave the desired products using Pd/C as the catalyst under high pressure (70 atm.).

Thus, (*R*)-**6a** afforded **14** and **15** in a ratio of 3:1. The stereochemistries of **14** and **15** were determined by NOE difference experiments (see double-headed arrow in formula **14**) (throughout this paper, the double-headed arrow symbol in a formula indicates significant NOE). Thus, the major product **14** resulted from attack of the catalyst on the bottom face of (*R*)-**6a**. The two-step conversion of **14** to (*R*)-**13** then indicates that the assigned structure of (*S*)-**6a** is the correct one. The same hydrogenation of (*S*)-**6a** also gave **16** and **12** in a 4:1 ratio.

Again, the major product **16** is the one corresponding to hydrogenation from the bottom face. The fact that the corresponding methyl ester [(±)-**6b**] gave a 1:1 mixture of two diastereomers **17** and **18** indicates that the replacement of the *l*-menthyl group with a methyl group results in an increase of the top face attack.

Reactions of 7 and 8. Conjugate addition of (*R*)-**7** with PhMgBr/CuI gave **19** as the sole product. By a two-step procedure (basic hydrolysis followed by methylation), **19** was converted to methyl (*R*)-3-hydroxy-3-phenylpropanoate [(*R*)-**20**].[17]

(5) Sato, M.; Sekiguchi, K.; Ogasawara, H.; Kaneko, C. *Synthesis* **1985**, 224−226. Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896−1901.

(6) Matsumoto, K.; Harada, K. *J. Org. Chem.* **1966**, *31*, 1956−1958.

(7) Jurczak, J.; Zamojski, A. *Rocz. Chem.* **1970**, *44*, 2557−2259.

(8) Bihlmayer, G. A.; Derkosch, J.; Polansky, O. E. *Monatsh. Chem.* **1967**, *98*, 564−578.

(9) Sato, M.; Yoneda, N.; Katagiri, N.; Watanabe, H.; Kaneko, C. *Synthesis* **1986**, 672−674.

(10) Sato, M.; Yoneda, N.; Kaneko, C. *Chem. Pharm. Bull.* **1986**, *34*, 4577−4584.

(11) Sato, M.; Ogasawara, H.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 2602−2608. (b) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087−2088.

(12) Carroll, M. F.; Bader, A. R. *J. Am. Chem. Soc.* **1952**, *74*, 6305; **1953**, *75*, 5400−5402.

(13) Detailed comparison of the 500 MHz ^{1}H NMR spectra of (*R*)- and (*S*)-**4a** indicated that both compounds have the same conformations as in the crystalline state. Thus, the isopropyl signals of (*S*)-**4a** appeared at a higher field (δ 0.468 and 0.714) than those (δ 0.564 and 0.783) of (*R*)-**4a**, while $6H_{equatorial}$ (*cis* to the isopropyl group) of (*R*)-**4a** appears at higher field (δ 1.788) than that (δ 1.834) of (*S*)-**4a**. Both upfield shifts can be explained by the shielding effect of the enone moiety of the dioxinone ring.

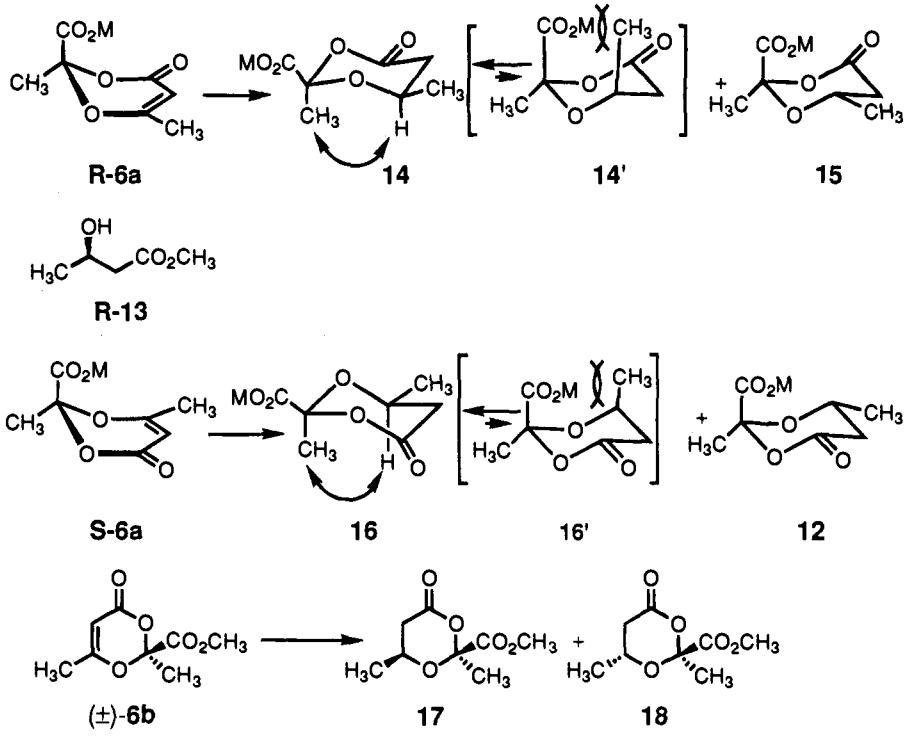
(14) When the *l*-menthyloxycarbonyl group takes an axial orientation in related dioxinones (e.g., **3a**), the signals of the *l*-menthyl group differ markedly, just as in **4a**. See ref 4.

(15) In the ^{1}H NMR spectra of **7** and **8**, the isopropyl groups in the *R*- and *S*-isomers exhibited almost the same signals. This fact indicates that the *l*-menthyl group in them is distant from the enone moiety.

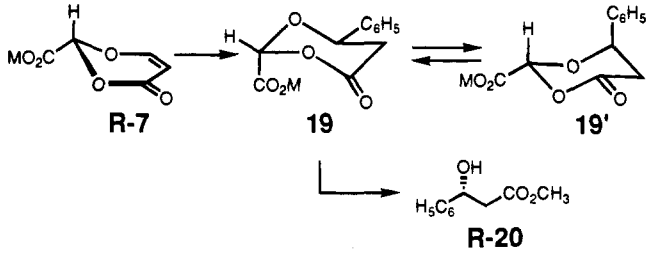
(16) Seebach, D.; Zuger, M. F. *Tetrahedron Lett.* **1984**, *25*, 2747−2750.

(17) For the *R*-isomer: Schopt, C.; Wust, W. *Justus Liebigs Ann. Chem.* **1959**, *626*, 150−154. For the *S*-isomer: Mitsui, K.; Konno, K.; Onuma, I.; Shimizu, K. *Nippon Kagaku Zasshi* **1964**, *85*, 437−440.

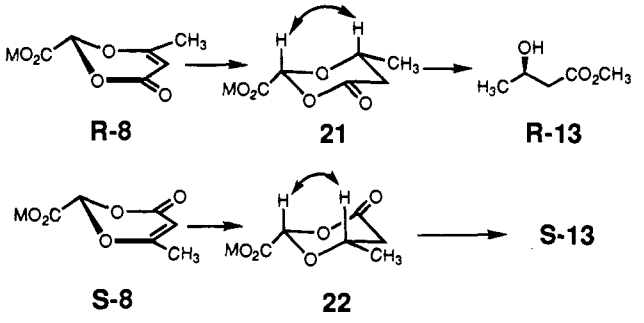
Scheme 2



Scheme 3



Scheme 4



The same top face preference was also observed in catalytic hydrogenation of **8**. Thus, (*R*)-**8** gave **21** as the sole product. The NOE experiment performed on **21** showed clearly that hydrogenation had proceeded again from the top face. Product **21** was converted to (*R*)-**13**. As expected, (*S*)-**8** gave **22** as the sole product, whose structure was verified by its conversion to (*S*)-**13**.

Origins of Sofa Conformation in the Hetero Ring, Pyramidalization of the Enone Function, and Facial Selectivity. The experimental data on conjugate addition and catalytic hydrogenation of **5**–**8** obtained in this work as well as those reported previously for related dioxinones **1**–**3**[2–4] are summarized in Table 2. The degrees of selectivity for the respective reactions are shown by ± (nearly 0% de), + (ca. 50% de), and +++ (100% de) in parentheses. The top of the table also shows the sofa conformation with the orientation of the 2-substituents deduced from X-ray crystallographic analyses of **1**, **2**, **3a**, and **4b** and from the observed facial selectivity in actual reactions. ^{1}H-NMR spectroscopic studies carried out on **3**–**8** also support the assigned conformations. As shown in Table 1, pyramidalization (toward the top face) of the enone function of **1**, **2**, and **4b** has been verified by X-ray crystallographic analyses.

From Table 2, it is evident that the conjugate addition to **1**, **2**, and **7a** occurs from the top face, while the same reaction occurs from the bottom face for **3a** and **5a**.

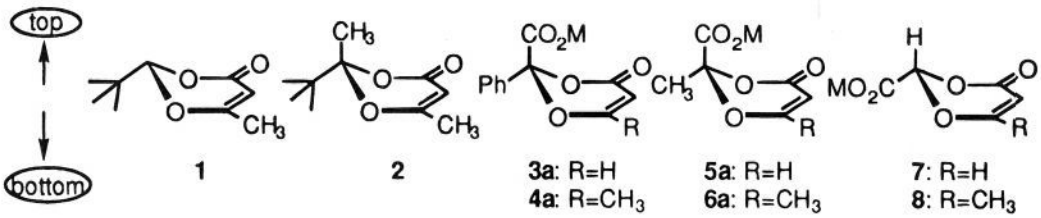
Seebach et al. have suggested that pyramidalization of the enone portion [(C(4) to C(6)] of the dioxinone **1** does not cause the stereoselectivity but that both phenomena have the same origin.[2] This proposal was accepted as reasonable by Lange et al. for the same reaction of **2**.[3] In other words, they considered that the reactions occur preferentially from the direction into which the center is pyramidalized. Their explanation, however, is not applicable to the conjugate addition to **3a** and **5a**, in which the nucleophile attacks from the opposite side. Though this preference can be explained in terms of the sofa conformation, the same explanation cannot be applied to the same reactions of **1**, **2**, and **7a**.

In order to analyze the results summarized in Table 2, we will discuss (1) the origin of the sofa conformation, (2) the origin of the pyramidalization, and (3) how these stereochemical features of dioxinones can be correlated with the facial selectivity.

Origin of the Sofa Conformation. We have already reported two interesting conformational characteristics of the oxazinedione **23** found by X-ray crystallographic analysis: (1) the molecule is in a boat conformation with C(2) and C(5) pointing upward and (2) the *p*-nitrophenyl group takes a quasi-axial orientation.[18] We explained the conformation at the 2-position of **23** in terms of a stabilizing interaction between

(18) Sato, M.; Nagashima, S.; Murakami, M.; Kaneko, C.; Furuya, T. *Tetrahedron* **1993**, *49*, 6575–6580.

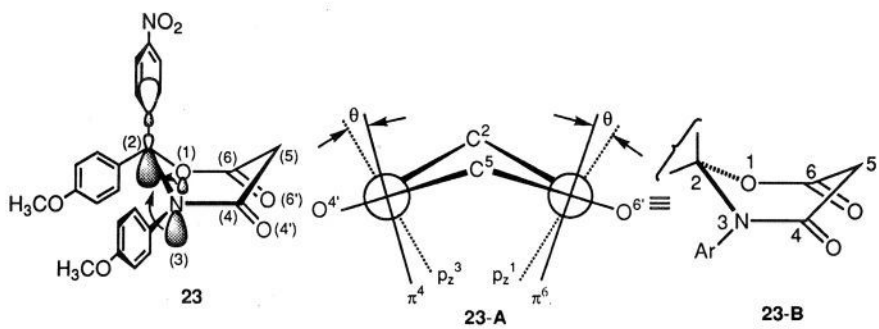
Table 2. Diastereofacial Selectivity of Conjugate Addition and Catalytic Hydrogenation of 1,3-Dioxin-4-ones



	1	2	3	5	7
conjugate addition (R_2CuLi)	top (+++)	top (+++)	bottom (+++)	bottom (+++)	top (+++)
	1	**2**	**4**	**6**	**8**
catalytic hydrogenation	top (+++)			bottom[a] (+)	top (+++)

[a] de becomes ± when **6b** (CH_3 instead of M) was used.

Chart 3



the lone pairs on N(3) and/or O(1) and the σ^* orbital on the axial C(2)−aryl bond. It is clear on energetic grounds that the stabilizing interaction between the lone-pair electrons on the heteroatoms and $\sigma^*_{p\text{-nitrophenyl(axial)}-C(2)}$ should be more important than that between the lone-pair electrons and the *p*-methoxyphenyl(axial)−C(2) bond in the hypothetical conformation whose two C(2) aryl groups are reversed from those of **23**. Hence, the stabilizing interaction depicted in **23** leads to an upward shift of the C(2) atom with the *p*-nitrophenyl group in an axial orientation.[19]

Connection of the Newman projections along the C(6)−O(1) and C(4)−N(3) bonds of the observed boat conformation results in **23-A**. The nitrogen and/or oxygen lone pairs (p_z orbitals: dotted lines) are perpendicular to the plane of C(2)−O(1)−C(6) and/or C(2)−N(3)−C(4) and the p_z orbitals (bold lines) of C(4) and C(6) are perpendicular to the O(1)−C(6)−C(5) and N(3)−C(4)−C(5) planes, respectively. From this figure, it is clear that the angles (θ) between the p_z-orbitals (O and N) and the p_z orbitals of C(4 and 6) are much smaller than the corresponding angles (θ') of the hypothetical chair conformation (cf. **23-B**). Thus, the boat conformation **23-A** is more likely to enjoy a stabilizing π-interaction between the heteroatoms and the C−O π-bonds.[20] In other words, if one considers only the above π-overlap, the ideal conformation is the one having θ equals to zero and hence corresponds to **23-B**, in which the C(2)−O(1) and C(6)=O bonds and C(2)−N(3) and C(4)=O bonds are parallel, respectively. In **23**, both C=O bonds are twisted toward the bottom side. In good accordance with the above considerations, X-ray crystallographic analyses of the dioxinones **3a** and **4b** revealed a sofa conformation with the alkoxycarbonyl group (an electron-withdrawing group) in a quasi-axial orientation. This should be because the $n_O-\sigma^*_{C-COOR}$ interaction (cf. **24**) is more important than the corresponding $n_O-\sigma^*_{C-Ph}$ interaction (note that σ^*_{C-COOR} is lower in energy and hence a better electron acceptor than σ^*_{C-Ph}).

When the two substituents on the acetal carbon are alkyl or hydrogen (cf. **1** and **2**), however, such a stereoelectronic effect becomes much smaller (note that $\sigma^*_{C-H/-alkyl}$ is higher in energy and hence cannot interact with n_O). Thus, one can conclude on purely steric grounds that 2-monoalkylated or 2,2′-dialkylated dioxinones should have the sofa conformation with the bulkier 2-substituent in an equatorial orientation.[21] In contrast, dioxinones with two substituents on the acetal carbon [C(2)] differing markedly in their electronic character should take a conformation with the more electronegative substituent in an axial orientation. Equatorial orientation of the *l*-menthyloxycarbonyl group in **7** and **8** indicates that the steric effect predominates over the electronic effect.

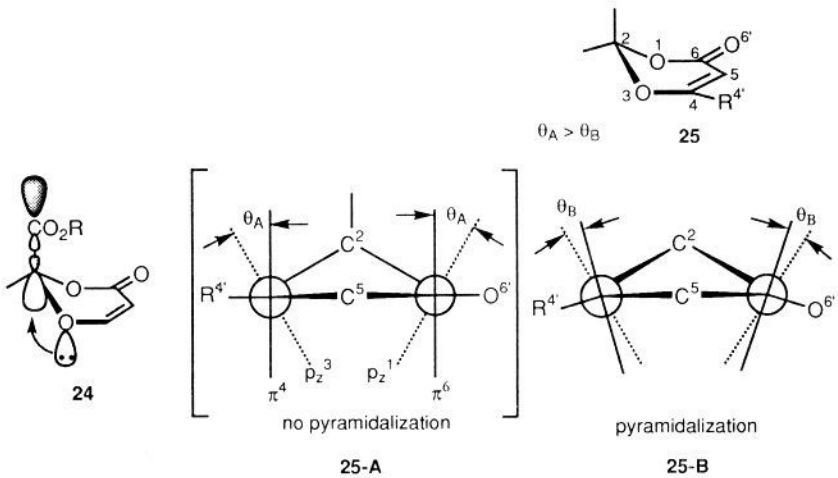
Pyramidalization. While there are other possible explanations for the origin and direction of the pyramidalization in all of the dioxinones **1**−**8**, the simplest one is the following. As we have already pointed out for the boat conformation of the

(19) The so-called anomeric effects are best explained in terms of n/σ^* interactions. (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983. (b) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; John Wiley & Sons, Inc.: New York, 1991.

(20) Somewhat similar proposals have been made in order to explain the boat conformation of a 1,6-dihydro-1,2,4,5-tetrazine derivative. Stam, C. H.; Counotte-Potman, A. D.; van der Plas, H. C. *J. Org. Chem.* **1982**, *47*, 2856−2858.

(21) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradon, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maeztke, T.; Mourino, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913−934.

Chart 4



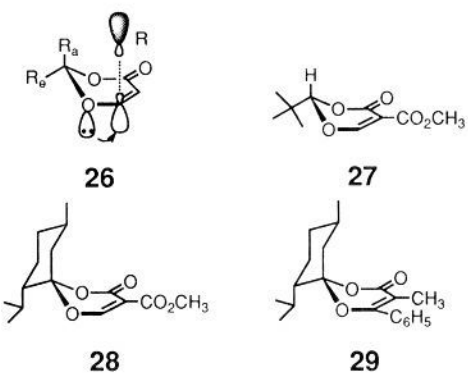
oxazinedione **23**, shifting of the acetal carbon to the top side (by either stereoelectronic or steric effects mentioned already) results in the same (top) side shift of C(5) in order to maximize the π-overlap in the O—C=O and N—C=O moieties. If this argument is applied to the O—C=O and O—C=C bonds in the dioxinone **25**, whose C(2) has already shifted to the top side, the C_6=O and C_4—R bonds are expected to twist toward the bottom side (cf. **25-A**). However, in contrast to the CO—CH_2—CO moiety in the oxazinediones **23**, the two unsaturated bonds in the dioxinone **25** are conjugated (C=C—C=O) and hence should be coplanar. In order to satisfy the above two requirements {(1) maximizing the π-conjugation of the five atoms [O_3—C_4=C_5—C_6(=O)—O_1] and (2) minimizing the corresponding angle θ (for the definition of θ, see **23-A** and its explanation)} at the same time, $O_{6'}$ and $R_{4'}$ should shift to the bottom side. In other words, the sp^2 carbons at the 4- and 6-positions should be pyramidalized toward the top side [the same side as C(2)] (cf. **25-B**).

Hence, we can conclude that the sofa conformation of the ring and pyramidalization of the enone portion [(C(4) to C(6)] of the dioxinone have the same origin and pyramidalization of C(6) is always in the same direction as that in which C(2) is shifted.

Origin of the Facial Selectivitity. How, then, can one explain why the conjugate addition to **1**, **2**, and **7** occurs from the top face, while the same reaction of **3a** and **5a** occurs from the bottom face? As noted already, neither sofa conformation nor pyramidalization can account for the facial selectivity.

We consider that facial selectivity in the conjugate addition reactions of the dioxinones is best explained by the so-called Cieplak theory.[22] Thus, for the dioxinones **1**, **2**, and **7**, the n_O lone-pair electrons interact with the antibonding orbital ($\sigma_{\ddagger}$*) of the incipient bond (C—R) (cf. **26**) and this hyperconjugation would cause the top face attack of the reagent (R). In **3**, the electron-withdrawing substituent (CO_2R) takes an axial orientation. Therefore, the lone-pair electrons of the oxygen atom in the dioxinone interact strongly with the antibonding orbital of $\sigma_{C(2)-COOR}$ (cf. **24**), and hence, the hyperconjugation facilitating the top face attack (cf. **26**) would become less effective.

Chart 5



In connection with the above explanation, it should be noted that Diels—Alder reaction of **27**[23] and its spiro analog **28**[24,25] and addition of molecular fluorine to spiro dioxinones[26] (e.g., **29**) proceed with high selectivity from the bottom face.

It is well-known that the steric demands of conjugate addition (in a more general sense, nucleophilic addition), pericyclic addition (e.g., Diels—Alder), and molecular fluorine addition reactions (in a more general sense, electrophilic addition) are significantly different from each other and the difference can be explained by the concept of "non-perpendicular attack". That is, the stabilizing HOMO—LUMO interaction in the transition state for an ionic attack on unsaturated bonds is maximized at a particular angle. Thus, nucleophilic attack occurs at an obtuse angle and electrophilic attack at an acute angle. That is, due to the unfavorable out-of-phase interaction between the attacking nucleophile and the carbonyl oxygen (a in **30'**), the nucleophile attacks at an angle of 109° (the "Burgi—Dunitz" angle, cf. **30**).[27]

(22) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540—4552. (b) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875—5876. (c) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447—8462.

(23) Sato, M.; Abe, Y.; Kaneko, C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1779—1783.

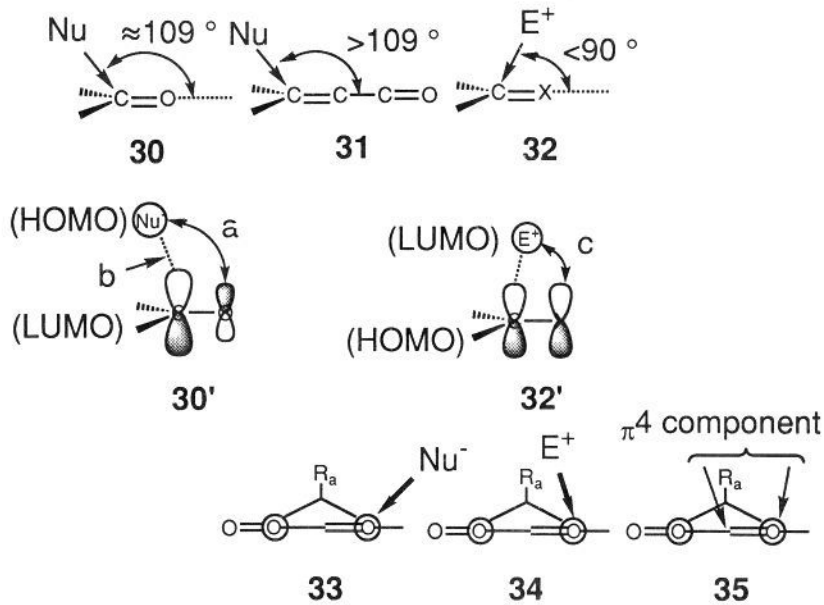
(24) (a) Sato, M.; Takayama, K.; Kaneko, C. *Chem. Pharm. Bull.* **1989**, *37*, 2615—2620. (b) Sato, M.; Orii, C.; Sakaki, J.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1989**, 1435—1436. (c) Iwaoka, T.; Katagiri, N.; Sato, M.; Kaneko, C. *Chem. Pharm. Bull.* **1992**, *40*, 2319—2324.

(25) We have already demonstrated that these spiro dioxinones behave in conjugate addition and catalytic hydrogenation exactly the same manner as **1** and **2**. Thus, in these reactions, the reagents attack from the top face. (a) Sato, M.; Takayama, K.; Furuya, T.; Inukai, N.; Kaneko, C. *Chem. Pharm. Bull.* **1987**, *35*, 3971—3974. (b) Kaneko, C.; Sato, M.; Sakaki, J.; Abe, Y. *J. Heterocycl. Chem.* **1990**, *27*, 25—30.

(26) Iwaoka, T.; Murohashi, T.; Sato, M.; Kaneko, C. *Tetrahedron: Asymmetry* **1992**, *3*, 1025—1028.

(27) (a) Burgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065—5067. (b) Burgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563—1572. (c) Burgi, H. B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460—473.

Chart 6



Due to the increase of out-of-phase interaction (a) relative to in-phase overlap (b), the angle increases further with conjugated enone systems **31**.[28,29] On the contrary, due to favorable in-phase interaction (c in **32′**), the angle becomes less than 90° for an electrophilic attack.[30] On this basis, the trajectories of the attacking reagents (Nu^- and E^+) to C(6) in dioxinones can be depicted as shown in formulas **33** and **34**. If the above argument is correct, it is clear that the unfavorable 1,3-diaxial interaction between the attacking reagent and the axial substituent on C(2) in the substrate is much larger in **34** than in **33**. This conclusion is in good accordance with the bottom face attack of molecular fluorine on **29**.[31] The bottom face preference for Diels–Alder reactions so far reported for all kinds of dioxinones is also explained by **35**, in which the steric demand is again significant for the top face attack.

Conclusions

For the ground-state reactions of the dioxinones, we conclude that top face preference is restricted to reactions having the least steric demand (e.g., nucleophilic reaction having an obtuse trajectory, cf. **33**) and to dioxinones having only an electron-donating substituent (e.g., hydrogen and alkyl) at the C(2)-axial position. For dioxinones having an electron-withdrawing substituent at C(2) in an axial orientation, all reactions proceed with bottom face preference. If the reaction has a significant steric demand (cf. **34** and **35**), the reverse face (the bottom face) preference is expected for all kinds of dioxinones.[32]

Experimental Section

General Procedures. All melting points are uncorrected. Optical rotations were measured with a JASCO DIP-340 digital polarimeter. IR spectra were measured on a JASCO A-102 spectrophotometer, and ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60 SI or JEOL JNM-GX 500 spectrometer with tetramethylsilane as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-DX-303 or JMS-AX-500 spectrometer. Wakogel (C-200) and Merck Kieselgel 60 F254 were employed for silica gel column chromatography and preparative thin layer chromatography (PTLC), respectively. The ratios of solvent mixtures for chromatography are shown as volume/volume.

***l*-Menthyl (2*R*)- and (2*S*)-6-Methyl-2-phenyl-4-oxo-1,3-dioxine-2-carboxylate ((*R*)-4a and (*S*)-4a).** A mixture of *l*-menthyl phenylglyoxylate (2.88 g, 10.0 mmol)[6] and 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**10**, 372 mg, 2.0 mmol)[11] in toluene (10.0 mL) was refluxed for 50 min. This mixture was subjected to silica gel column chromatography (hexane–ethyl acetate (20:1)) to give the starting ester (2.48 g). Further elution with hexane–ethyl acetate (1:1) gave a mixture of (*R*)- and (*S*)-**4a** (ca. 1:1, 468 mg, 63% yield based on **10**) as a solid. Fractional recrystallization of this mixture from hexane gave less soluble (*R*)-**4a** (200 mg) and more soluble (*S*)-**4a** (170 mg).

(*R*)-4a: mp 84–85 °C, needles; $[\alpha]_D^{26}$ +26.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.564 (3H, d, *J* = 6.5 Hz, isopropyl Me), 0.780–0.910 (1H, m, $C_{4'}$-axial H), 0.783 (3H, d, *J* = 6.5 Hz, isopropyl Me), 0.853 (3H, d, *J* = 6.5 Hz, $C_{5'}$-Me), 0.881 (1H, q, *J* = 11.5 Hz, $C_{6'}$-axial H), 0.977 (1H, dq, *J* = 13.0, 3.0 Hz, $C_{3'}$-axial H), 1.402 (1H, tt, *J* = 11.5, 3.0 Hz, $C_{2'}$-H), 1.370–1.480 (1H, m, $C_{5'}$-axial H), 1.565 (1H, dh, *J* = 7.0, 3.0 Hz, C*H*Me_2), 1.620–1.680 (2H, m, $C_{3'}$- and $C_{4'}$-equatorial H), 1.788 (1H, ddt, *J* = 11.5, 4.0, 2.0 Hz, $C_{6'}$-equatorial H), 2.180 (3H, d, *J* = 1.0 Hz, C_6-Me), 4.687 (1H, dt, *J* = 11.0, 4.5 Hz, $C_{1'}$-H), 5.397 (1H, d, *J* = 1.0, C_5-H), 7.410–7.460 and 7.715–7.750 (5H, m, phenyl); IR ($CHCl_3$) 1750 (br), 1630 cm^{-1}; MS *m/z* 359 (M^+ + 1), 175, 139. Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.88; H, 7.73.

(*S*)-4a: mp 70–71 °C, prisms; $[\alpha]_D^{26}$ −112.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.468 and 0.714 (each 3H, d, *J* = 7.0 Hz, isopropyl Me), 0.833 (1H, dq, *J* = 14.0, 4.0 Hz, $C_{4'}$-axial H), 0.873 (3H, d, *J* = 6.5 Hz, $C_{5'}$-Me), 0.995 (H, dq, *J* = 13.0, 3.0 Hz, $C_{3'}$-axial H), 1.017 (1H, q, *J* = 12.0 Hz, $C_{6'}$-axial H), 1.350 (1H, dh, *J* = 7.0, 3.0 Hz, $CHMe_2$), 1.389 (1H, tt, *J* = 11.0, 3.0 Hz, $C_{2'}$-H), 1.370–1.480 (1H, m, $C_{5'}$-axial H), 1.834 (1H, ddt, *J* = 12.0, 3.5, 2.0 Hz, $C_{6'}$-equatorial H), 2.180 (3H, d, *J* = 1.0, $C_{6'}$-Me), 4.686 (1H, dt, *J* = 11.0, 4.5 Hz, $C_{1'}$-H), 5.392 (1H, s, C_5-H), 7.405–7.460 and 7.755–7.720 (5H, m, phenyl); IR ($CHCl_3$) 1755, 1640 cm^{-1}; MS *m/z* 373 (M^+ + 1), 189, 139. Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.88; H, 7.73.

Methyl (±)-6-Methyl-2-phenyl-4-oxo-1,3-dioxine-2-carboxylate [(±)-4b]. A mixture of methyl phenylglyoxylate (3.28 g, 20.0 mmol) and **10** (1.86 g, 10.0 mmol) in toluene (20.0 mL) was refluxed for 2 h.

(28) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139–145.

(29) Mikami, K.; Shimizu, M. *Advances in Detailed Reaction Mechanisms*; JAI Press Inc.: Greenwich, CT, 1994; Vol. 3, pp 45–77.

(30) (a) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162–7166. (b) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263–268.

(31) The addition of molecular fluorine to ethylene was concluded to be electrophilic in nature on the basis of *ab initio* MO calculation[31a] and deduction from experimental data.[31b] (a) Iwaoka, T.; Kaneko, C.; Shigihara, A.; Ichikawa, H. *J. Phys. Org. Chem.* **1993**, *6*, 195. (b) Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307–312.

(32) Photo[2 + 2]cycloadditions of these dioxinones to alkenes take place generally with the bottom face preference. Though we did not mention its mechanism, the bottom side preference would be mostly due to the steric factor, since steric demand in the corresponding transition states would be very similar to that (**35**) of [4 + 2]cycloaddition.

The solvent was evaporated *in vacuo*, and the residue was subjected to silica gel column chromatography with hexane–ethyl acetate (10:1) to give first the starting ester (2.30 g) and then (±)-**4b** (1.33 g, 54%) as a solid. Recrystallization from a mixture of hexane and ether gave needles of mp 78–79 °C: ^{1}H NMR ($CDCl_3$) δ 2.17 (3H, s, C_6-Me) 3.76 (3H, s, OMe), 5.40 (1H, s, C_5-H), 7.19–7.94 (5H, m, phenyl); IR ($CHCl_3$) 1755, 1735, 1635 cm^{-1}; MS *m/z* 189 ($M^+ - 59$). Anal. Calcd for $C_{12}H_{12}O_5$: C, 62.90; H, 7.58. Found: C, 62.82; H, 7.62.

***l*-Menthyl (2*R*)- and (2*S*)-2-Methyl-4-oxo-1,3-dioxine-2-carboxylate ((*R*)-5a and (*S*)-5a).** 5-Formyl-1,3-dioxane-4,6-dione (**9**, 1.72 g, 10.0 mmol)[8] was added over 30 min to a refluxing solution of *l*-menthyl pyruvate[6] (6.78 g, 30.0 mmol) in toluene (150 mL). Refluxing was continued for an additional 4 h, then the solvent was evaporated *in vacuo*. The residue was subjected to silica gel column chromatography with hexane–ethyl acetate (20:1) to give first the pyruvate and then a mixture of (*R*)- and (*S*)-**5a** (ca. 1:1, 6.78 g, 76%) as a solid. Fractional recrystallization from pentane gave less soluble (*S*)-**5a** and more soluble (*R*)-**5a**.

(*R*)-5a: mp 92–93 °C, needles; $[\alpha]_D^{26}$ −132.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.717 (3H, d, *J* = 7.0 Hz, isopropyl Me), 0.882 (H, dq, *J* = 13.0, 4.0 Hz, $C_{4'}$-axial H), 0.898 (3H, d, *J* = 7.0 Hz, isopropyl Me), 0.916 (3H, d, *J* = 6.5 Hz, $C_{5'}$-Me), 1.030 (1H, q, *J* = 11.5 Hz, $C_{6'}$-axial H), 1.042 (1H, m, $C_{5'}$-axial H), 1.670–1.740 (2H, m, $C_{3'}$-equatorial H), 4.771, (1H, dt, *J* = 11.0, 4.5 Hz, $C_{1'}$-H), 5.467 and 7.258 (each 1H, d, *J* = 5.5 Hz); IR ($CHCl_3$) 1765, 1755, 1620 cm^{-1}; MS *m/z* 296 ($M^+ + 1$), 139, 113. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.67; H, 8.04.

(*S*)-5a: mp 109–111 °C, needles; $[\alpha]_D^{26}$ +23.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.739 (3H, d, *J* = 6.5 Hz, isopropyl Me), 0.884 (1H, dq, *J* = 13.0, 3.5 Hz, $C_{4'}$-axial H), 0.897 (3H, d, *J* = 6.5 Hz, isopropyl Me), 0.909 (3H, d, *J* = 6.0 Hz, $C_{5'}$-Me), 1.044 (1H, q, *J* = 12.0 Hz, $C_{6'}$-axial H), 1.044 (1H, q, *J* = 12.0 Hz, $C_{6'}$-axial H), 1.491 (1H, tt, *J* = 12.0, 3.0 Hz, $C_{2'}$-H), 1.440–1.540 (1H, m, $C_{5'}$-axial H), 1.660–1.730 (2H, m, $C_{3'}$-and $C_{4'}$-equatorial H), 1.793 (1H, dh, *J* = 7.0, 3.0 Hz, C*H*Me$_2$), 1.838 (3H, s, C_2-Me), 1.936 (1H, ddt, *J* = 11.5, 4.5, 2.0 Hz, $C_{6'}$-equatorial H) 4.775 (1H, dt, *J* = 11.0, 4.5 Hz, $C_{1'}$-H), 5.470 and 7.240 (each 1H, d, *J* = 6.0 Hz); IR ($CHCl_3$) 1765, 1755, 1620 cm^{-1}; MS *m/z* 297 ($M^+ + 1$), 139, 113. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.03; H, 8.11.

***l*-Menthyl (2*R*)- and (2*S*)-2,6-Dimethyl-4-oxo-1,3-di-oxine-2-carboxylate ((*R*)-6a and (*S*)-6a).** A mixture of *l*-menthyl pyruvate (4.52 g, 20.0 mmol) and **10** (3.72 g, 20.0 mmol) in toluene (40.0 mL) was refluxed for 90 min. The solvent was evaporated *in vacuo*. Purification of the residue by silica gel column chromatograpy with hexane–ethyl acetate (30:1) gave a mixture of (*R*)- and (*S*)-**6a** (*ca.* 1:1, 5.10 g, 82% yield) as a solid. Fractional recrystallization from a mixture of hexane and ether gave less soluble (*R*)-**6a** and more soluble (*S*)-**6a**.

(*R*)-6a: mp 89–90 °C, prisms; $[\alpha]_D^{26}$ −62.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.710 (3H, d, *J* = 6.9 Hz, isopropyl Me) 0.873 (1H, dq, *J* = 12.0, 3.2 Hz, $C_{4'}$-axial H), 0.894 (3H, d, *J* = 6.9 Hz, isopropyl Me), 0.913 (3H, d, *J* = 6.8 Hz, $C_{5'}$-Me), 0.994 (1H, q, *J* = 11.5 Hz, $C_{6'}$-axial H), 1.034 (1H, dq, *J* = 12.5, 3.2 Hz, $C_{3'}$-axial H), 1.420–1.540 (1H, m, $C_{5'}$-axial H), 1.467 (1H, tt, *J* = 11.5, 3.2 Hz, $C_{2'}$-H), 1.670–1.730 (2H, m, $C_{3'}$-and $C_{4'}$-equatorial H), 1.808 (1H, dh, *J* = 3.5, 6.9 Hz, C*H*Me$_2$), 1.819 (3H, s, C_2-Me), 1.940 (1H, ddt, *J* = 11.5, 3.5, 2.0 Hz, $C_{6'}$-equatorial H), 2.057 (3H, d, *J* = 1.0, C_6-Me), 4.739 (1H, dt, *J* = 11.0, 4.3 Hz, $C_{1'}$-H), 5.276 (1H, q, *J* = 1.0 Hz, C_6-H); IR ($CHCl_3$) 1770, 1740, 1630 cm^{-1}; MS *m/z* 311 ($M^+ + 1$), 139, 127. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.86; H, 8.39.

(*S*)-6a: mp 84–85 °C, plates; $[\alpha]_D^{26}$ −51.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.736 (3H, d, *J* = 7.4 Hz, isopropyl Me) 0.878 (1H, dq, *J* = 12.6, 3.5 Hz, $C_{4'}$-axial H), 0.896 (3H, d, *J* = 7.4 isopropyl Me), 0.905 (3H, d, *J* = 6.2 Hz, $C_{5'}$-Me), 1.038 (1H, dq, *J* = 13.0, 3.5 Hz, $C_{3'}$-axial H), 1.055 (1H, q, *J* = 12.1 Hz, $C_{6'}$-axial H), 1.425–1.525 (1H, m, $C_{5'}$-axial H), 1.479 (1H, tt, *J* = 11.8, 3.1 Hz, $C_{2'}$-H), 1.655–1.720 (2H, m, $C_{3'}$-and $C_{4'}$-equatorial H), 1.771 (1H, dh, *J* = 3.5, 7.4 Hz, C*H*Me$_2$), 1.820 (3H, s, C_2-Me), 1.903 (1H, ddt, *J* = 12.1, 4.0, 2.0 Hz, $C_{6'}$-equatorial H), 2.052 (3H, d, *J* = 1.0 Hz, C_6-Me), 4.771 (1H, dt, *J* = 11.2, 4.5 Hz, $C_{1'}$-H), 5.272 (1H, q, *J* = 1.0 Hz, C_5-H); IR ($CHCl_3$) 1770, 1740, 1640 cm^{-1}; MS *m/z* 311 ($M^+ + 1$), 139, 127. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.81; H, 8.47.

Methyl (±)-2,6-Dimethyl-4-oxo-1,3-dioxine-2-carboxylate [(±)-6b]. A mixture of methyl pyruvate (1.02 g, 10.0 mmol) and **10** (1.86 g, 10.0 mmol) in toluene (20.0 mL) was refluxed for 3 h. The solvent was evaporated *in vacuo*, and the residue was distilled under vacuum to give (±)-**6b** (1.49 g, 80%) as an oil of bp 72 °C (0.01 Torr): ^{1}H NMR ($CDCl_3$) δ 1.83 (3H, s, C_2-Me), 2.05 (3H, s, C_6-Me), 3.80 (3H, s, OMe), 5.23 (1H, s, C_5-H); IR ($CHCl_3$) 1760, 1740, 1640 cm^{-1}; MS *m/z* 186 (M^+). Anal. Calcd for $C_8H_{10}O_5$: C, 51.61; H, 4.51. Found: C, 51.70; H, 5.44.

***l*-Menthyl (2*R*)- and (2*S*)-4-Oxo-1,3-dioxine-2-carboxylate ((*R*)-7 and (*S*)-7).** Compound **9** (2.58 g, 15.0 mmol) was added over 30 min to a refluxing solution of *l*-menthyl glyoxylate (2.30 g, 10.0 mmol)[7] in toluene (100 mL). The solution was refluxed for an additional 1.5 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (20:1) to give a mixture of (*R*)- and (*S*)-**7** (ca.1:1, 2.13 g, 76% yield) as a solid. Fractional recrystallization of this mixture from pentane gave less soluble (*R*)-**7**. The mother liquor was purified on a Merck Lobar column (hexane-ether (20:1)) to give more soluble (*S*)-**7**, which was recrystallized from pentane.

(*R*)-7: mp 85–86 °C, needles; $[\alpha]_D^{26}$ −176.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.755 (3H, d, *J* = 7.0 Hz, isopropyl Me) 0.896 (1H, dq, *J* = 12.5, 3.0 Hz, $C_{4'}$-axial H), 0.907 (3H, d, *J* = 7.0 isopropyl Me), 0.928 (3H, d, *J* = 7.0 Hz, $C_{5'}$-Me), 1.067 (1H, dq, *J* = 12.0, 4.0 Hz, $C_{5'}$-axial H), 1.086 (1H, q, *J* = 12.0 Hz, $C_{6'}$-axial H), 1.491 (1H, tt, *J* = 11.5, 4.0, 2.0 Hz, $C_{2'}$-H), 1.4460–1.560 (1H, m, $C_{5'}$-axial H), 1.680–1.750 (2H, m, $C_{3'}$- and $C_{4'}$-equatorial H), 1.855 (1H, dh, *J* = 7.0, 3.0 Hz, C*H*Me$_2$), 2.019 (1H, ddt, *J* = 11.5, 4.0, 2.0 Hz, $C_{6'}$-equatorial H), 4.865 (1H, dt, *J* = 11.5, 4.0 Hz, $C_{1'}$-H), 5.552 (1H, d, *J* = 6.0 Hz, C_5-H), 5.908 (1H, s, C_2-H), 7.346 (1H, d, *J* = 6.0 Hz, C_6-H); IR ($CHCl_3$) 1765, 1755, 1641 cm^{-1}; MS *m/z* 283 ($M^+ + 1$), 139. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: 63.81; H, 7.74.

(*S*)-7: mp 48–49 °C, needles; $[\alpha]_D^{26}$ +41.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.757 (3H, d, *J* = 6.5 Hz, isopropyl Me) 0.893 (1H, dq, *J* = 12.0, 3.0 Hz, $C_{4'}$-axial H), 0.906 (3H, d, *J* = 6.5 Hz, isopropyl Me), 0.924 (3H, d, *J* = 6.5 Hz, $C_{5'}$-Me), 1.069 (1H, dq, *J* = 13.0, 4.0 Hz, $C_{3'}$-axial H), 1.093 (1H, q, *J* = 11.5 Hz, $C_{6'}$-axial H), 1.494 (1H, tt, *J* = 11.5, 3.0 Hz, $C_{2'}$-H), 1.480–1.580 (1H, m, $C_{5'}$-axial H), 1.675–1.745 (2H, m, $C_{3'}$- and $C_{4'}$-equatorial H), 1.844 (1H, dh, *J* = 3.0, 7.0 Hz, C*H*Me$_2$), 2.023 (1H, ddt, *J* = 12.0, 4.0, 2.0 Hz, $C_{6'}$-equatorial H), 4.863 (1H, dt, *J* = 5.5, 4.5 Hz, $C_{1'}$-H), 5.552 (1H, d, *J* = 5.5 Hz, C_5-H), 5.908 (1H, s, C_2-H), 7.334 (1H, d, *J* = 5.5 Hz, C_6-H); IR ($CHCl_3$) 1765, 1755, 1610 cm^{-1}; MS *m/z* 283 ($M^+ + 1$), 139. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: 63.58; H, 7.78.

***l*-Menthyl (2*R*)- and (2*S*)-6-Methyl-4-oxo-1,3-dioxine-2-carboxylate ((*R*)-8 and (*S*)-8).** A solution of 2,2,6-trimethyl-1,3-dioxin-4-one (**11**, 1.85 g, 13.0 mmol)[12] in toluene (5 mL) was added over 10 min to a refluxing solution of *l*-menthyl glyoxylate (2.30 g, 10.0 mmol). The solution was refluxed for an additional 2.5 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (20:1) to give a mixture of (*R*)- and (*S*)-**8** (*ca.* 1:1, 2.70 g, 91%) as a solid. Fractional recrystallization from pentane–ether gave less soluble (*R*)-**8** and more soluble (*S*)-**8**.

(*R*)-8: mp 84–85 °C, needles; $[\alpha]_D^{25}$ −139.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.750 (3H, d, *J* = 7.0 Hz, isopropyl Me) 0.889 (1H, dq, *J* = 13.0, 4.0 Hz, $C_{4'}$-axial H), 0.928 (6H, d, *J* = 7.0, 3.2 Hz, isopropyl Me and $C_{5'}$-Me), 1.064 (1H, dq, *J* = 11.0, 3.0 Hz, $C_{3'}$-axial H), 1.069 (1H, q, *J* = 11.0 Hz, $C_{6'}$-axial H), 1.480 (1H, tt, *J* = 11.0, 3.0 Hz, $C_{2'}$-H), 1.493 (1H, m, $C_{5'}$-axial H), 1.670–1.740 (2H, m, $C_{3'}$- and $C_{4'}$-equatorial H), 1.857 (1H, dh, *J* = 7.0, 3.0 Hz, C*H*Me$_2$), 2.011 (1H, m, $C_{6'}$-equatorial H), 2.104 (3H, d, *J* = 1.0 Hz, C_6-Me), 4.842 (1H, dt, *J* = 11.0, 4.0 Hz, $C_{1'}$-H), 5.343 (1H, q, *J* = 1.0, C_5-H), 5.864 (1H, s, C_2-H); IR ($CHCl_3$) 1750, 1740, 1630 cm^{-1}; MS *m/z* 297 ($M^+ + 1$), 139. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.88; H, 8.13.

(*S*)-8: mp 69–70 °C, needles; $[\alpha]_D^{22}$ +13.8 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.763 (3H, d, *J* = 7.4 Hz, isopropyl Me) 0.891 (1H, dq, *J* = 13.0, 4.0 Hz, $C_{4'}$-axial H), 0.904 (3H, d, *J* = 7.0 Hz, isopropyl Me), 0.921 (3H, d, *J* = 7.0 Hz, $C_{5'}$-Me), 1.068 (1H, dq, *J* = 13.0, 4.0 Hz, $C_{3'}$-axial H), 1.095 (1H, q, *J* = 11.0 Hz, $C_{6'}$-axial H), 1.485 (1H, tt, *J* = 11.5, 3.0 Hz, $C_{2'}$-H), 1.460–1.560 (1H, m, $C_{5'}$-H), 1.670–1.740

(2H, m, $C_{3'}$- and $C_{4'}$-equatorial H), 1.831 (1H, dh, J = 7.0, 3.0 Hz, C*H*Me_2), 2.005 (1H, ddt, J = 12.0, 4.0, 2.0 Hz, $C_{6'}$-equatorial H), 2.099 (3H, d, J = 1.0 Hz, C_6-Me), 4.849 (1H, dt, J = 11.0, 4.0, Hz, $C_{1'}$-H), 5.345 (1H, q, J = 1.0 Hz, C_5-H), 5.866 (1H, s, C_2-H); IR ($CHCl_3$) 1750, 1740, 1630 cm^{-1}; MS *m/z* 297 (M^+ + 1), 139. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.72; H, 8.14.

***l*-Menthyl (2*S*,6*R*)-2,6-Dimethyl-4-oxo-1,3-dioxane-2-carboxylate (12).** A solution of methylmagnesium bromide (1 M THF solution, 1.5 mL, 1.5 mmol) was added to a stirred mixture of CuI (285 mg, 1.5 mmol) and dry THF (5 mL) at −78 °C, and the whole was stirred at −78 °C for 30 min. A solution of (*S*)-**5a** (148 mg, 0.50 mmol) in dry THF (3 mL) was added to the mixture, and the whole was stirred at −78 °C for 20 min. Saturated NH_4Cl solution was added to the mixture, and the whole was extracted with ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Purification of the residue by PTLC with hexane−ethyl acetate (5:1) gave **12** (108 mg, 70% yield) as a solid. Recrystallization from pentane gave prisms of mp 122−123 °C: $[\alpha]_D^{26}$ −91.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.761 and 0.911 (each 3H, d, J = 7.0 Hz, CH*Me*$_2$), 0.921 (3H, d, J = 6.5 Hz, $C_{5'}$-Me), 2.359 (1H, dd, J = 18.0, 10.5 Hz, C_5-H), 4.018 (1H, ddq, J = 10.5, 4.0, 6.5 Hz, C_6-H), 4.751 (1H, dt, J = 11.0, 4.5 Hz, $C_{1'}$-H); IR ($CHCl_3$) 1755, 1735 cm^{-1}; MS *m/z* 225 (M^+ − 87), 139. Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.59; H, 8.95.

Hydrolysis of 12 to give (*R*)-13. A solution of **12** (156 mg, 0.50 mmol) and potassium hydroxide (81 mg, 1.5 mmol) in methanol (4 mL) and water (1 mL) was heated at 50 °C for 5 min. The solvent was evaporated *in vacuo*. The residue was acidified with dilute HCl and then diluted with THF. The solution was dried over $MgSO_4$ and evaporated, and the residue was treated with ethereal diazomethane. Evaporation of the solvent left an oil, which was purified by silica gel column chromatography with hexane−ethyl acetate (2:1) to give (*R*)-**13** (51 mg, 86% yield from (*S*)-**5a**). The ^1H NMR data and specific rotation [$[\alpha]_D^{22}$ −44.2 °C (*c* 1.0, $CHCl_3$)] were identical with those of a commercial sample.[16]

***l*-Menthyl (2*R*,6*R*)- and (2*R*,6*S*)-2,6-Dimethyl-4-oxo-1,3-dioxane-2-carboxylate (14 and 15).** Compound (*R*)-**6a** (100 mg, 0.32 mmol) was hydrogenated in ethyl acetate (20 mL) with 10% Pd/C (30 mg) under 70 atm at 45 °C for 3 d. Removal of the catalyst and the solvent left a mixture of **14** and **15** (ca. 3:1 based on ^1H NMR analysis) as a solid (101 mg, 100% yield). Fractional recrystallization from a mixture of pentane and ether gave an analytical sample of **14**. When this hydrogenation was conducted at 0 °C, the ratio of **14/15** was ca. 6 as shown by ^1H NMR analysis.

14: mp 81−82 °C, prisms; $[\alpha]_D^{23}$ −16.4 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.756 and 0.900 (each 3H, d, J = 7.0 Hz, CH*Me*$_2$), 0.920 (3H, d, J = 6.0 Hz, $C_{5'}$-Me), 1.358 (3H, d, J = 6.0 Hz, C_6-Me), 1.718 (3H, s, C_2-Me), 2.475 (1H, dd, J = 17.5, 11.5 Hz, C_5-H), 2.647 (1H, dd, J = 17.5, 3.5 Hz, C_5-H), 4.288 (1H, m, C_6-H), 4.746 (1H, dt, J = 11.5, 4.5 Hz, $C_{1'}$-H); IR ($CHCl_3$) 1740 cm^{-1}; MS *m/z* 225 (M^+ − 87). Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.18; H, 9.01.

15: ^1H NMR ($CDCl_3$) δ 0.747 and 0.908 (each 3H, d, J = 7.0 Hz, CH*Me*$_2$), 0.924 (3H, d, J = 6.0, $C_{5'}$-Me), 1.324 (3H, d, J = 6.0 Hz, C_6-Me), 1.728 (3H, s, C_2-Me), 2.360 (1H, dd, J = 17.5, 10.5 Hz, C_5-H), 2.636 (1H, dd, J = 17.5, 4.0 Hz, C_5-H), 4.025 (1H, m, C_6-H) 4.739 (1H, dt, J = 10.5, 4.0 Hz, $C_{1'}$-H).

By following the procedure given for the transformation of **12** to (*R*)-**13**, compound **14** (62.4 mg, 0.20 mmol) was hydrolyzed and then methylated to give (*R*)-**13** [19 mg, 80% yield, $[\alpha]_D^{22}$ −45.1 (*c* 1.0, $CHCl_3$)].

***l*-Menthyl (2*S*,6*S*)- and (2*S*,6*R*)-2,6-Dimethyl-4-oxo-1,3-dioxane-2-carboxylate (16 and 12).** By following the above procedure, (*S*)-**6a** (100 mg, 0.32 mmol) was hydrogenated to give a mixture of **16** and **12** (ca. 4:1 based on ^1H NMR analysis) as a solid (101 mg, 100% yield). Recrystallization from a mixture of pentane and ether gave **16** as needles of mp 92−93 °C: $[\alpha]_D^{21}$ −242 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.762 and 0.899 (each 3H, d, J = 7.0 Hz, CH*Me*$_2$), 0.919 (3H, d, J = 6.0 Hz, $C_{5'}$-Me), 1.357 (3H, d, J = 6.0, Hz, C_6-Me), 1.717 (3H, s, C_2-Me), 2.471 (1H, dd, J = 17.5, 11.5 Hz, C_5-H), 2.649 (1H, dd, J = 17.5, 3.5 Hz, C_5-H), 4.288 (1H, ddq, J = 11.5, 3.5, 6.0 Hz, C_6-H), 4.750 (1H, dt, J = 11.0, 4.5 Hz, $C_{1'}$-H); IR ($CHCl_3$) 1740 cm^{-1}; MS *m/z* 225 (M^+ − 87). Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.70; H, 9.07.

Methyl (2*S,6*S**)- and (2*S**,6*R**)-2,6-Dimethyl-oxo-1,3-dioxane-2-carboxylate (17 and 18).** Compound (±)-**6b** (186 mg, 1.0 mmol) was hydrogenated in ethyl acetate (20 mL) with 10% Pd/C (100 mg) under 70 atm at 40 °C for 2 d to give a mixture of **17** and **18** (1:1 based on ^1H NMR analysis) as an oil (183 mg, 97% yield). Chromatography with a Lobar column using hexane−ethyl acetate (10:1) gave **17** (more polar) and **18** (less polar).

17: ^1H NMR ($CDCl_3$) δ 1.336 (3H, d, J = 6.2 Hz), 1.725 (3H, s), 2.467 (1H, dd, J = 17.6, 11.4 Hz), 2.642 (1H, dd, J = 17.6, 3.7 Hz), 3.834 (3H, s), 4.283 (1H, ddq, J = 11.4, 3.7, 6.2 Hz; IR ($CHCl_3$) 1755 cm^{-1}; HRMS *m/z* 189.0770 (M^+ + H, $C_8H_{13}O_5$ requires 189.0763).

18: ^1H NMR ($CDCl_3$) δ 1.326 (3H, d, J = 6.0 Hz), 1.746 (3H, s), 2.368 (1H, dd, J = 17.5, 11.0 Hz), 2.658 (1H, dd, J = 17.5, 4.0 Hz), 3.834 (3H, s), 4.037 (1H, ddq, J = 11.0, 4.0, 6.0 Hz); IR ($CHCl_3$) 1755 cm^{-1}; HRMS *m/z* 189.0772 (M^+ + H, $C_8H_{13}O_5$ requires 189.0763).

***l*-Menthyl (2*R*)-6-Phenyl-4-oxo-1,3-dioxane-2-carboxylate (19).** By following the procedure given for the preparation of **12** from (*S*)-**5a**, (*R*)-**7** (282 mg, 1 mmol) was treated with phenylmagnesium bromide in ether to give crude **19** as an oil. A solution of this oil and potassium hydroxide (168 mg, 3.0 mmol) in methanol (3 mL) and water (1 mL) was heated at 50 °C for 15 min. After evaporation of the solvent, the residue was extracted with pentane to remove *l*-menthol. The aqueous layer was acidified with dilute HCl and extracted with ether. The organic layer was dried over $MgSO_4$ and then evaporated. The residue was treated with ethereal diazomethane under ice-cooling. Evaporation of the solvent followed by purification by PTLC with $CHCl_3$ gave (*R*)-**20** (77 mg, 47% from (*R*)-**7**) as an oil: $[\alpha]_D^{26}$ +16.3° (*c* 4.60, EtOH).[17]

***l*-Menthyl (2*R*,6*R*)-6-Methyl-4-oxo-1,3-dioxane-2-carbox-ylate (21).** Compound (*R*)-**8** (148 mg, 0.5 mmol) was hydrogenated with 10% Pd/C (50 mg) in ethyl acetate under 50 atm at 45 °C for 2 d. Removal of the catalyst and the solvent left **21** (148 mg, 99% yield) as an oil: $[\alpha]_D^{21}$ −76.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.771 and 0.899 (each 3H, d, J = 7.0 Hz, CH*Me*$_2$), 0.919 (3H, d, J = 7.0 Hz, $C_{5'}$-Me), 1.421 (3H, d, J = 6.0 Hz, C_6-Me), 2.559 (1H, dd, J = 18.0, 11.0 Hz, C_5-H), 4.138 (1H, m, C_6-H), 4.830 (1H, dt, J = 11.0, 4.0 Hz, $C_{1'}$-H), 5.607 (1H, s, C_2-H); IR ($CHCl_3$) 1760 cm^{-1}; HRMS *m/z* 298.1788 (M^+, requires 298.1780). By following the procedure given for conversion of **12** to (*R*)-**13**, **21** was transformed into (*R*)-**13** [72% yield, $[\alpha]_D$ −42.6 (*c* 0.7, $CHCl_3$)].

***l*-Menthyl (2*S*,6*S*)-6-Methyl-4-oxo-1,3-dioxane-2-carboxylate (22).** By the above procedure, (*S*)-**8** (100 mg, 0.33 mmol) was hydrogenated to give **22** (101 mg, 100% yield) as a solid. Recrystallization from pentane gave needles of mp 74−75 °C: $[\alpha]_D^{22}$ −38.8 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.771, 0.898 (each 3H, d, J = 7.0 Hz, CH*Me*$_2$), 0.919 (3H, d, J = 7.0 Hz, $C_{5'}$-Me), 1.424 (3H, d, J = 6.0 Hz, C_6-Me), 2.563 (1H, dd, J = 18.0, 11.0 Hz, C_5-H), 2.728 (1H, dd, J = 18.0, 4.0 Hz, C_5-H), 4.142 (1H, m, C_6-H), 4.829 (1H, dt, J = 11.0, 4.0 Hz, $C_{1'}$-H) 5.612 (1H, s, C_2-H); IR ($CHCl_3$) 1760 cm^{-1}; MS *m/z* 298 (M^+). Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.29; H, 8.76. By following the procedure given for conversion of **12** to (*R*)-**13**, **22** was transformed into (*S*)-**13** [78% yield, $[\alpha]_D^{22}$ +43.5 (*c* 0.8, $CHCl_3$)].

X-ray Crystal Structure Determination of (±)-4b. A columnar crystal of $C_{13}H_{12}O_5$ having approximate dimensions of 0.5 × 0.5 × 0.5 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite-monochromated Cu Kα radiation and a 12 kW rotating anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range 75.80° < 2θ < 79.82° corresponded to a primitive monoclinic cell with dimensions a = 8.628(1) Å, b = 12.4009(9) Å, c = 23.081(1) Å, β = 99.432(7)°, and V = 2436.1(3) Å.[3] For Z = 8 and fw = 248.23, the calculated density is 1.01 g/cm^3. The systematic absences of *h*0*l* ($l \neq 2n$) and 0*k*0 ($k \neq 2n$) uniquely determine the space group to be $P2_1/c$ ($\neq$14). The data were collected at a temperature of 23 ± 1 °C using the ω−2θ scan technique to a maximum 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.26° with a take-off angle of 6.0°. Scans of (1.73 + 0.14

tan θ)° were made at a speed of 32.0 deg/min (in ω). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of three scans), and the counts were accumulated to ensure good counting statistics. Of the 4098 reflections which were collected, 3814 were unique ($R_{int} = 0.025$). The linear absorption coefficient, μ, for Cu $K\alpha$ radiation is 6.7 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods[33] and expanded using Fourier techniques.[34] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final R and R_w values were 4.2 and 3.6%, respectively. All calculations were performed using the teXsan[35] crystallographic software package of Molecular Structure Corp.

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Supplementary Material Available: Text and tables giving full details of the X-ray crystallographic analysis (27 pages); listing of structure factors (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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